Journal of Fluorine Chemistry 154 (2013) 73–79

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Synthesis of fluorinated pyrimidinones

Mikhail D. Kosobokov [a], Marina I. Struchkova [a], Dmitry E. Arkhipov [b], Alexander A. Korlyukov [b], Alexander D. Dilman [a,*]

[a] N.D. Zelinsky Institute of Organic Chemistry, Leninsky prosp. 47, 119991 Moscow, Russian Federation
[b] A.N. Nesmeyanov Institute of Organoelement Compounds, Vavilov str. 28, 119991 Moscow, Russian Federation

ARTICLE INFO

Article history:
Received 22 May 2013
Received in revised form 25 June 2013
Accepted 30 June 2013
Available online 10 July 2013

Keywords:
Heterocycles
Isocyanates
Cyclization
Pyrimidinones
Coupling reaction

ABSTRACT

A method for the construction of fluorinated pyrimidinones based on the reaction of cyanodifluoromethyl-substituted amines with isocyanates is described. The use of *ortho*-iodophenylisocyanate in this reaction followed by copper catalyzed intramolecular amination affords fluorinated fused heterocycles – 4-fluoropyrimido[1,6-*a*]benzimidazol-1(2*H*)-ones.

1. Introduction

The ability of fluorine to modify biological properties of organic compounds has sparked the interest to partially fluorinated molecules [1]. Since heterocycles are ubiquitous in pharmaceuticals, compounds containing one or two fluorine atoms in the ring have gained significant attention in medicinal chemistry [2]. Among diverse classes of fluorinated heterocycles, derivatives of pyrimidinones and pyrimidinediones have become particularly important exhibiting anti-cancer, antiviral, and antifungal activity [1b,2b,3,4]. Fluorinated uracil and cytosine were the first examples of successful drugs of this type followed by numerous analogs (Fig. 1). The conventional synthetic approach toward mono- and difluorinated pyrimidinones involves fluorination of parent heterocycles using elemental fluorine or O–F and N–F reagents [5,6]. An alternative method for the preparation of difluoro-substituted pyrimidinediones (dihydrouracils) based on building-block strategy was suggested, but the method has a limited scope [7].

Herein we describe a general approach for making fluorinated six-membered heterocycles based on coupling of three components – imines, difluoroacetonitrile carbanion, and a reagent with electrophilic multiple bond (Scheme 1). Thus, we have recently described that imines react with difluoro(trimethylsilyl)acetonitrile leading to products **1** [8]. The latter compounds possess a nucleophilic amine and an electrophilic nitrile group, and reaction of this 1,4-bipolar system with an appropriate double or triple bond is expected to afford heterocyclic molecule. In this work we demonstrate this concept by using isocyanates as the AB component [9]. The process affords pyrimidinones (A = CO, B = NR^3) bearing *N*-unsubstituted imino-function, which can be further exploited for constructing more complex heterocyles.

2. Results and discussion

First, the reactions of amines **1** with isocyanates were investigated (Table 1). Due to the presence of fluorine atoms

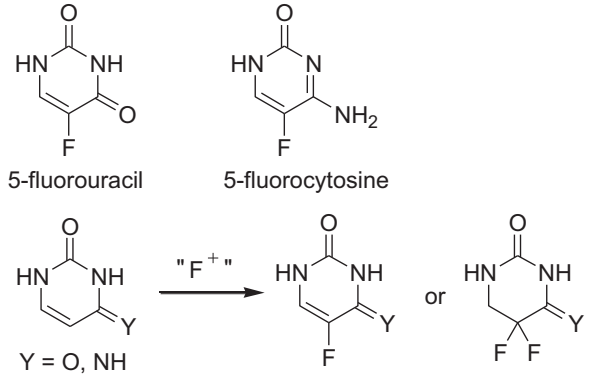
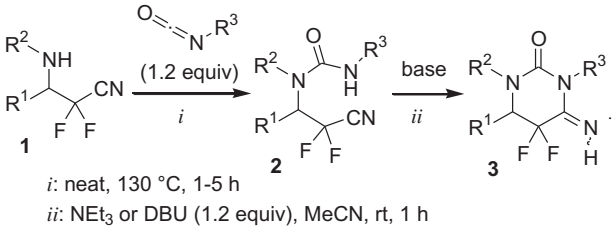


Fig. 1. Fluorinated pyrimidinones.

* Corresponding author. fax: +7 499 1355328.
E-mail addresses: adil25@mail.ru, dilman@ioc.ac.ru (A.D. Dilman).

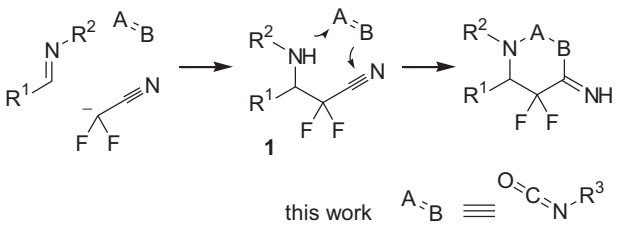
0022-1139/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jfluchem.2013.06.018

Table 1
Reaction of 3-amino-2,2-difluoropropanenitriles with isocyanates.

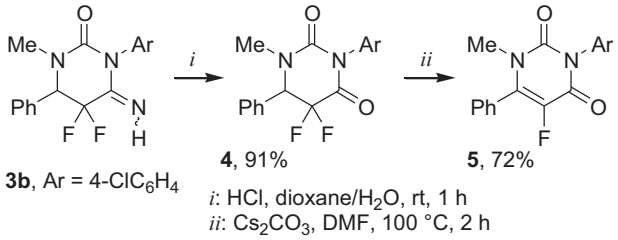


R^1	R^2	R^3	1	2	Time for **1**→**2**, h	Yield of **2**,[a] %	3	Base	Yield of **3**,[a] %
Ph	Me	Ph	**1a**	**2a**	3	95	**3a**	NEt_3	95
Ph	Me	4-ClC_6H_4	**1a**	**2b**	1	95	**3b**	NEt_3	97
	Bn	Ph	**1b**	**2c**	3	83	**3c**	NEt_3	98
	Bn	4-ClC_6H_4	**1b**	**2d**	3	80[b]	**3d**	NEt_3	99
Ph	Me	Pr	**1a**	**2e**[c]	5	93	**3e**	DBU	78

[a] Isolated yield.
[b] Additionally, *ca.* 10% of heterocycle **3d** was formed.
[c] Performed using 3 equiv. of PrNCO.



Scheme 1. Approach to six-membered heterocycles.



Scheme 2. Synthesis of fluorouracil **5**.

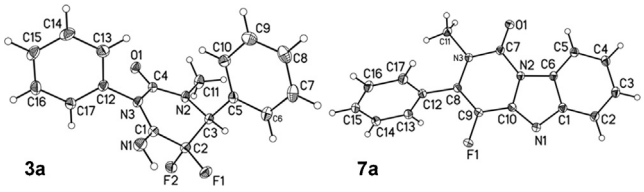
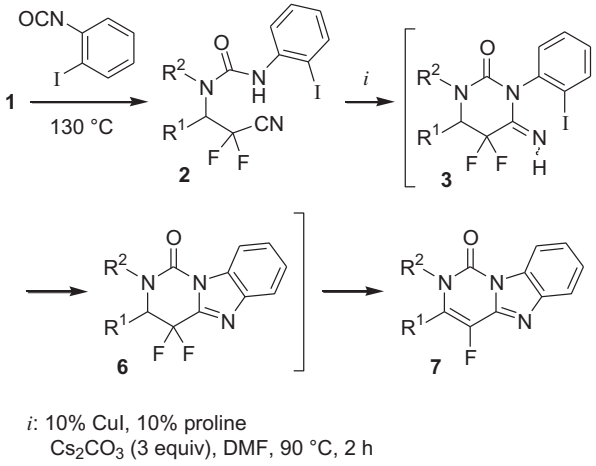


Fig. 2. The molecular structures of compounds 3a (left) and 7a (right). Non-hydrogen atoms are presented by thermal ellipsoids at 50% probability.

Table 2
Synthesis of fused heterocycles **7**.



R^1	R^2	1	2	Time for **1**→**2**, h	Yield of **2**,[a] %	7	Yield of **7**,[a] %
Ph	Me	**1a**	**2f**	2	94	**7a**	81
	Bn	**1b**	**2g**	5	67	**7b**	80
	Me	**1c**	**2h**	2	96	**7c**	77
1-Naphthyl	Me	**1d**	**2i**	2	95	**7d**	79
4-$MeOC_6H_4$	Et	**1e**	**2j**	3	92	**7e**[b]	75

[a] Isolated yield.
[b] Reaction time 5 h.

and cyano group, amines **1** have decreased nucleophilicity and, contrary to regular secondary *N*,*N*-dialkylamines, required heating at 130 °C with isocyanates in the absence of solvent. The ureas **2** were isolated in excellent yield and purity, except urea **2d**, which contained about 10% of cyclized heterocycle **3d**. Cyclization of ureas **2a-d** into iminopyrimidinones **3a–d** occurred readily and quantitatively in the presence of triethylamine (1.2 equiv.). However, urea **2e** bearing an *N*-propyl substituent did not react under standard conditions, and employment of a stronger base 1,8-diazabicycloundec-7-ene (DBU) was necessary to obtain product **3e**. In solution compounds **3** exist as mixtures of geometrical isomers owing to the C=N bond, whereas X-ray analysis of a single crystal of the heterocycle **3a** showed only one isomer (Fig. 2) [10]. When crystals corresponding to one isomer, for which the structure was determined by X-ray analysis, were dissolved in $CDCl_3$, ^{19}F NMR spectrum showed two isomers. This fact suggests that inversion of nitrogen lone pair within the C=N–H fragment has moderate activation barrier, and, as a result, the position of equilibrium between geometrical isomers may depend on the medium.

The opportunity to synthesize fluorouracils was exemplified by transformation of the iminopyrimidinone **3b** (Scheme 2). Thus, the imino group of **3b** was hydrolyzed under acidic conditions to give the dione **4**, from which one fluorine was eliminated in the presence of Cs_2CO_3 furnishing 5-fluoro-substituted uracil **5**.

To demonstrate the utility of the present methodology for accessing more complex fluorinated heterocycles, we decided to exploit functionalization of the N–H group of the iminopyrimidinones. The use of isocyanate bearing iodine in *ortho*-position provides ureas **2** (Table 2). It was found that heating of iodo-substituted ureas **2** at 90 °C in the presence of Cs_2CO_3 and catalytic amounts of CuI and proline [11] afforded monofluorinated fused 4-fluoropyrimido[1,6-*a*]benzimidazol-1(2*H*)-ones **7** in good yields. The reaction likely involves copper catalyzed cyclization [11] of iminopyrimidinones **3** generating intermediate **6** followed by elimination of HF. To support this mechanism, we were able to isolate difluorinated heterocycle **6e** when the copper catalyzed coupling was performed at 50 °C. The structure of the heterocycle **7a** was verified by X-ray analysis (Fig. 2) [10]. Thus, we have demonstrated that our isocyanate/coupling sequence constitutes a straightforward construction of pyrimido [1,6-*a*]benzimidazol-1(2*H*)-one heterocycles [12].

3. Conclusions

We have disclosed a convenient method for assembling difluorinated iminopyrimidinones from isocyanates and secondary amines originating from imines and difluoro(trimethylsilyl)acetonitrile. This methodology can be used for the synthesis of 5-fluorouracil derivatives, as well as for construction of fluoro-substituted fused heterocycles.

4. Experimental

4.1. General experimental procedures

All reactions were performed under an argon atmosphere. Acetonitrile was distilled from CaH_2 and stored under molecular sieves 4 Å. DMF was distilled under vacuum from P_2O_5 and stored over MS 4 Å. Column chromatography was carried out employing silica gel (230–400 mesh). For NMR measurements, $CDCl_3$ was distilled from CaH_2. Coupling constants (*J*) are given in Hz. NMR spectra were recorded on a Bruker AM-300 instrument. Microanalyses were performed on KarloErba 1106 instrument. High resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and time-of-flight (TOF) mass analyzer. The measurements were done in a positive ion mode (interface capillary voltage – 4500 V) or in a negative ion mode (3200 V); mass range from *m*/*z* 50 to *m*/*z* 3000 Da. 2,2-Difluoro-3-(methylamino)-3-phenylpropanenitrile (**1a**) and difluoro(trimethylsilyl)acetonitrile were obtained according to literature procedures [8]. 2-Iodophenylisocyanate was obtained from 2-iodoaniline and diphosgene [13]. Imines were obtained by condensation of aldehydes and imines [14]. Other chemicals were commercially available (Aldrich, Acros) and were used as-received. Column chromatography was carried out employing Merck silica gel (Kieselgel60, 230–400 mesh). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography visualizing with UV and/or acidic aq. $KMnO_4$ solution. For microscale distillation, the provided boiling points correspond to bath temperature.

4.2. Synthesis of amines ***1b-e***

CF_3CO_2H (0.96 mL, 12.5 mmol) was added to a mixture of imine (10 mmol) and KHF_2 (580 mg, 7.5 mmol) in acetonitrile (30 mL) at 0 °C, and the suspension was stirred for 5 min. Difluoro(trimethylsilyl)acetonitrile (2.24 g, 15 mmol) was added, and the mixture was stirred for 18 h at room temperature. Saturated aqueous Na_2CO_3 (20 mL) was added dropwise, the mixture was stirred for 2 min, diluted with water (150 mL) and extracted with ether/hexane (1/1, 3 × 50 mL). The combined organic phase was filtered through Na_2SO_4, concentrated, and the residue was purified by chromatography (hexanes/EtOAc).

4.2.1. 3-(Benzylamino)-2,2-difluoro-3-thien-2-ylpropanenitrile (***1b***)

Yield: 2.14 g (7.7 mmol, 77%). Colorless crystals. mp 27–28 °C, bp 123–130 °C (bath temp)/0.2 Torr. Chromatography (hexanes/EtOAc 20/1 → 15/1), R_f 0.30 (hexanes/EtOAc 20/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.16 (s, 1H), 3.89 (d, 1H, *J* = 13.2), 4.09 (d, 1H, *J* = 13.2), 4.52 (dd, 1H, *J* = 12.6, 7.9), 7.15–7.22 (m, 1H), 7.23–7.29 (m, 1H), 7.40–7.52 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 50.9, 60.8 (t, *J* = 25.4), 110.9 (t, *J* = 248.8), 111.8 (t, *J* = 45.3), 127.0, 127.2, 127.5, 128.2, 128.3, 128.5, 135.0 (d, *J* = 2.2), 138.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −94.8 (dd, *J* = 286.1, 7.9), −100.2 (dd, *J* = 286.1, 12.6). Calcd for $C_{14}H_{12}F_2N_2S$: C, 60.42; H, 4.35; N, 10.07. Found: C, 60.69; H, 4.14; N, 10.28.

4.2.2. 2,2-Difluoro-3-(2-furyl)-3-(methylamino)propanenitrile (***1c***)

Yield: 1.24 g, (6.7 mmol, 67%). Colorless oil. bp 94–101 °C (bath temp)/12 Torr. Chromatography (hexanes/EtOAc 20/1 → 10/1), R_f 0.44 (hexanes/EtOAc 10/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.72 (s, 1H), 2.50 (s, 3H), 4.13 (dd, 1H, *J* = 12.6, 8.3), 6.42–6.45 (m, 1H), 6.49–6.52 (m, 1H), 7.47–7.50 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.7, 62.4 (dd, *J* = 24.8, 25.8), 110.6 (t, *J* = 249.9), 110.65, 110.72, 111.8 (t, *J* = 44.9), 143.7, 146.2 (d, *J* = 3.5). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −100.2 (dd, *J* = 286.1, 12.6), −95.9 (dd, *J* = 286.1, 8.3). Calcd for $C_8H_8F_2N_2O$: C, 51.61; H, 4.33; N, 15.05. Found: C, 51.75; H, 4.39; N, 15.19.

4.2.3. 2,2-Difluoro-3-(methylamino)-3-(1-naphthyl)propanenitrile (***1d***)

Yield: 1.82 g (7.4 mmol, 74%). Colorless oil. bp 140–145 °C (bath temp)/0.25 Torr. Chromatography (hexanes/EtOAc 10/1 → 5/1), R_f 0.38 (hexanes/EtOAc 10/1). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.91 (s, 1H), 2.54 (s, 3H), 5.08 (t, 1H, *J* = 9.3), 7.54–7.71 (m, 3H), 7.84–7.91 (m, 1H), 7.94–8.01 (m, 2H), 8.11–8.18 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.9, 62.6 (t, *J* = 25.3), 112.0 (t, *J* = 44.9), 112.7 (t, *J* = 249.9), 122.4, 125.3, 125.5, 126.0, 126.8, 128.9 (d, *J* = 3.5), 129.1, 130.0, 132.4, 133.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −97.4 (dd,

J = 288.2, 9.3), −92.8 (dd, J = 288.2, 9.3). Calcd for $C_{14}H_{12}F_2N_2$: C, 68.28; H, 4.91; N, 11.38. Found: C, 68.27; H, 4.80; N, 11.28.

4.2.4. 3-(Ethylamino)-2,2-difluoro-3-(4-methoxyphenyl)propanenitrile (**1e**)

Yield: 1.73 g (7.2 mmol, 72%). Colorless oil. bp 112–120 °C (bath temp)/0.8 Torr. Chromatography (hexanes/EtOAc 20/1 → 10/1), R_f 0.45 (hexanes/EtOAc 10/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.13 (t, 3H, J = 7.3), 1.54 (s, 1H), 2.61–2.77 (m, 2H), 3.84 (s, 3H), 4.10 (t, 1H, J = 10.1), 6.96 (d, 2H, J = 8.8), 7.37 (d, 2H, J = 8.8). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.1, 42.1, 55.2, 66.0 (t, J = 24.2), 112.0 (t, J = 45.5), 112.1 (t, J = 248.2), 114.3, 125.0 (d, J = 3.5), 129.7, 160.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −99.2 (dd, J = 286.1, 10.1), −95.7 (dd, J = 286.1, 10.1). Calcd for $C_{12}H_{14}F_2N_2O$: C, 59.99; H, 5.87; N, 11.66. Found: C, 60.02; H, 5.81; N, 11.77.

4.3. Reaction of amines **1** with arylisocyanates (general procedure)

A mixture of amine **1** (1 mmol) and isocyanate (1.2 mmol) was heated at 130 °C during a certain time (3 h for **2a**,**c**,**d**,**j**; 1 h for **2b**; 2 h for **2f**,**h**,**i**; 5 h for **2g**). After cooling, the mixture was subjected to column chromatography (hexanes/EtOAc).

4.3.1. N-(2-Cyano-2,2-difluoro-1-phenylethyl)-N-methyl-N′-phenylurea (**2a**)

Yield: 300 mg (0.95 mmol, 95%). Colorless crystals. mp 128–130 °C. Chromatography (hexanes/EtOAc 5/1), R_f 0.43 (hexanes/EtOAc 5/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.88 (s, 3H), 6.56 (dd, 1H, J = 13.9, 16.5), 6.85 (s, 1H), 7.07–7.15 (m, 1H), 7.27–7.36 (m, 2H), 7.40–7.51 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.8, 59.5 (dd, J = 23.0, 25.1), 110.9 (dd, J = 251.1, 253.1), 111.8 (t, J = 44.4), 120.8, 124.0, 128.6 (t, J = 1.7), 128.8, 129.1, 129.2, 130.8, 138.1, 155.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −95.4 (dd, J = 292.5, 16.5), −93.2 (dd, J = 292.5, 13.9). Calcd for $C_{17}H_{15}F_2N_3O$: C, 64.75; H, 4.79; N, 13.33. Found: C, 64.87; H, 4.68; N, 13.31.

4.3.2. N′-(4-Chlorophenyl)-N-(2-cyano-2,2-difluoro-1-phenylethyl)-N-methylurea (**2b**)

Yield: 332 mg (0.95 mmol, 95%). Colorless crystals. mp 141–144 °C. Chromatography (hexanes/EtOAc 3/1), R_f 0.44 (hexanes/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.88 (s, 3H), 6.50 (dd, 1H, J = 16.7, 13.1), 6.82 (s, 1H), 7.25 (d, 2H, J = 8.8), 7.36 (d, 2H, J = 8.8), 7.41–7.51 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.9, 59.6 (t, J = 23.6), 110.8 (t, J = 252.3), 111.8 (t, J = 44.4), 122.0, 128.6, 128.9, 129.1, 129.2, 129.3, 130.6, 136.7, 155.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −95.5 (dd, J = 292.5, 16.7), −93.5 (dd, J = 292.5, 13.1). Calcd for $C_{17}H_{14}ClF_2N_3O$: C, 58.38; H, 4.03; N, 12.01. Found: C, 58.43; H, 4.06; N, 12.10.

4.3.3. N-Benzyl-N-(2-cyano-2,2-difluoro-1-thien-2-ylethyl)-N′-phenylurea (**2c**)

Yield: 330 mg (0.83 mmol, 83%). Colorless crystals. mp 109–113 °C. Chromatography (hexanes/EtOAc 4/1), R_f 0.25 (hexanes/EtOAc 4/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.71 (s, 2H), 6.60 (br, 1H), 7.02–7.53 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 48.4, 56.4 (t, J = 24.2), 110.2 (t, J = 252.2), 111.5 (t, J = 44.3), 120.1, 123.8, 126.2, 127.4, 128.0, 128.4, 128.7, 129.4, 129.9, 131.4, 135.6, 137.8, 155.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −95.9 (dd, J = 286.1, 14.8), −94.8 (dd, J = 286.1, 14.8). HRMS (ESI) Calcd for $C_{21}H_{18}F_2N_3OS$ (M+H): 398.1133. Found: 398.1133.

4.3.4. N-Benzyl-N′-(4-chlorophenyl)-N-(2-cyano-2,2-difluoro-1-thien-2-ylethyl)urea (**2d**)

Yield: 388 mg (0.90 mmol) of the mixture of **2d** and **3d** (*ca.* 9:1), which corresponds to the 80% yield of **2d**. Colorless crystals. mp 112–114 °C. Chromatography (hexanes/EtOAc 3/1), R_f 0.44 (hexanes/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.68 (s, 2H), 6.55 (br, 1H), 6.92–7.57 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 48.3, 56.5 (t, J = 24.2), 110.1 (t, J = 252.2), 111.5 (t, J = 43.8), 121.3, 126.2, 127.5, 128.0, 128.4, 128.6, 128.8, 129.4, 129.9, 131.2, 135.4, 136.4, 155.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −95.9 (dd, J = 287.2, 14.8), −94.8 (dd, J = 287.2, 14.8). HRMS (ESI) Calcd for $C_{21}H_{17}ClF_2N_3OS$ (M+H): 432.0738. Found: 432.0743.

4.3.5. N-(2-Cyano-2,2-difluoro-1-phenylethyl)-N-methyl-N′-propylurea (**2e**)

A mixture of amine **1a** (196 mg, 1 mmol) and propylisocyanate (255 mg, 3 mmol) was heated in a tightly closed test tube for 5 h at 130 °C. After cooling to room temperature, the excess of isocyanate was evaporated under vacuum, and the residue was purified by chromatography (hexanes/EtOAc, 5/1). Yield: 261 mg (0.93 mmol, 93%). Colorless oil. Chromatography (hexanes/EtOAc 5/1 → 3/1), R_f 0.22 (hexanes/EtOAc 5/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.90 (t, 3H, J = 7.3), 1.48–1.62 (m, 2H), 2.72 (s, 3H), 3.17–3.31 (m, 2H), 5.10 (t, 1H, J = 4.8), 6.48 (dd, 1H, J = 17.5, 12.8), 7.34–7.43 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.0, 23.1, 30.1, 42.9, 59.5 (dd, J = 22.5, 24.8), 111.1 (dd, J = 251.1, 253.4), 111.8 (t, J = 44.9), 128.4, 128.80, 128.83, 131.1, 158.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −95.9 (dd, J = 290.3, 17.5), −92.9 (dd, J = 290.3, 12.8). HRMS (ESI) Calcd for $C_{14}H_{17}F_2N_3ONa$ (M+Na): 304.1237. Found: 304.1232.

4.3.6. N-(2-Cyano-2,2-difluoro-1-phenylethyl)-N′-(2-iodophenyl)-N-methylurea (**2f**)

Yield: 415 mg (0.94 mmol, 94%). Colorless crystals. mp 118–120 °C. Chromatography (hexanes/EtOAc 3/1), R_f 0.22 (hexanes/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.03 (s, 3H), 6.59 (t, 1H, J = 15.3), 6.84 (t, 1H, J = 7.3), 7.12 (s, 1H), 7.30–7.56 (m, 6H), 7.78 (d, 1H, J = 7.3), 8.22 (d, 1H, J = 7.3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.1, 59.5 (t, J = 24.2), 90.6, 110.7 (dd, J = 250.9, 259.0), 111.7 (t, J = 44.4), 121.6, 125.4, 128.6 (t, J = 1.7), 129.15, 129.20, 129.26, 130.7, 138.5, 138.6, 155.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −95.2 (dd, J = 292.5, 15.3), −93.4 (dd, J = 292.5, 15.3). Calcd for $C_{17}H_{14}F_2IN_3O$: C, 46.28; H, 3.20; N, 9.52. Found: C, 46.26; H, 3.12; N, 9.53.

4.3.7. N-Benzyl-N-(2-cyano-2,2-difluoro-1-thien-2-ylethyl)-N′-(2-iodophenyl)urea (**2g**)

Yield: 350 mg (0.67 mmol, 67%). Colorless crystals. mp 27–28 °C. Chromatography (hexanes/EtOAc 10/1 → 5/1), R_f 0.17 (hexanes/EtOAc 5/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.81 (s, 2H), 6.74–6.83 (m, 1H), 6.88 (s, 1H), 7.00–7.17 (m, 2H), 7.22–7.50 (m, 8H), 7.63–7.69 (m, 1H), 8.05–8.11 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 48.3, 56.6 (t, J = 24.2), 89.7, 110.0 (t, J = 252.2), 111.5 (t, J = 44.3), 122.2, 125.3, 126.2, 127.3, 128.0, 128.1, 128.8, 129.1, 130.0, 131.0, 135.0, 138.6, 138.9, 155.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −95.8 (dd, J = 288.2, 14.8), −94.6 (dd, J = 288.2, 14.8). Calcd for $C_{21}H_{16}F_2IN_3OS$: C, 48.20; H, 3.08; N, 8.03. Found: C, 48.35; H, 3.18; N, 7.94.

4.3.8. N-[2-Cyano-2,2-difluoro-1-(2-furyl)ethyl]-N′-(2-iodophenyl)-N-methylurea (**2h**)

Yield: 414 mg (0.96 mmol, 96%). Colorless crystals. mp 91–93 °C (hexanes). Chromatography (hexanes/EtOAc 3/1), R_f 0.20 (hexanes/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.18 (s, 3H), 6.43–6.73 (m, 3H), 6.84 (t, 1H, J = 7.3), 7.08–7.18 (br, 1H), 7.37 (t, 1H, J = 7.3), 7.50–7.60 (br, 1H), 7.78 (d, 1H, J = 7.3), 8.21 (d, 1H, J = 7.3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.3, 55.1 (t, J = 25.3), 90.3, 109.4 (t, J = 252.2), 110.7, 111.4 (t, J = 43.8), 112.5, 121.4, 125.3, 129.3, 138.5, 138.6, 143.6, 144.2, 154.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −96.8 (dd, J = 290.3, 13.3), −95.4 (dd, J = 290.3, 13.3). Calcd for $C_{15}H_{12}F_2IN_3O_2$: C, 41.78; H, 2.81; N, 9.75. Found: C, 41.87; H, 2.77; N, 9.71.

*4.3.9. N-[2-Cyano-2,2-difluoro-1-(1-naphthyl)ethyl]-N′-(2-iodophenyl)-N-methylurea (**2i**)*

Yield: 466 mg (0.95 mmol, 95%). Colorless crystals. mp 132–134 °C (hexanes/EtOAc 1/1). Chromatography (hexanes/EtOAc 3/1 → 1/1), R_f 0.25 (hexanes/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.95 (s, 3H), 6.88 (t, 1H, J = 7.3), 7.06 (br, 1H), 7.18 (dd, 1H, J = 16.1, 13.6), 7.44 (t, 1H, J = 7.3), 7.54–7.67 (m, 3H), 7.79 (d, 1H, J = 7.3), 7.88 (d, 1H, J = 7.3), 7.91–8.03 (m, 2H), 8.14 (d, 1H, J = 8.1), 8.33 (d, 1H, J = 8.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.8, 56.8 (t, J = 23.0), 90.6, 111.2 (dd, J = 250.5, 253.4), 112.0 (t, J = 43.8), 121.8, 123.0, 124.7, 125.4, 126.6, 127.0 (br), 128.0, 129.1, 129.4, 130.7, 131.7, 134.1, 138.6, 138.8, 154.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −95.9 (dd, J = 290.3, 16.1), −93.2 (dd, J = 290.3, 13.6). Calcd for $C_{21}H_{16}F_2IN_3O$: C, 51.34; H, 3.28; N, 8.55. Found: C, 51.18; H, 3.19; N, 8.58.

*4.3.10. N-[2-Cyano-2,2-difluoro-1-(4-methoxyphenyl)ethyl]-N-ethyl-N′-(2-iodophenyl)urea (**2j**)*

Yield: 446 mg (0.92 mmol, 92%). Colorless crystals. mp 46–49 °C (Et_2O). Chromatography (hexanes/EtOAc 3/1), R_f 0.30 (hexanes/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.16 (t, 3H, J = 6.6), 3.41–3.51 (m, 2H), 3.83 (s, 3H), 6.51 (t, 1H, J = 15.5), 6.82 (t, 1H, J = 7.3), 6.98 (d, 2H, J = 8.4), 7.12 (s, 1H), 7.36 (t, 1H, J = 7.3), 7.47 (d, 2H, J = 8.4), 7.77 (d, 1H, J = 8.1), 8.27 (d, 1H, J = 8.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 38.9, 55.1, 59.2 (t, J = 24.2), 89.9, 110.8 (t, J = 251.1), 111.8 (t, J = 43.8), 114.5, 121.4, 122.8, 125.0, 129.1, 130.4, 138.5, 138.8, 154.5, 160.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −94.7 (d, 2F, J = 15.5). Calcd for $C_{19}H_{18}F_2IN_3O_2$: C, 47.03; H, 3.74; N, 8.66. Found: C, 46.94; H, 3.84; N, 8.58.

*4.4. Synthesis of heterocycles **3a**–**d** (general procedure)*

Triethylamine (825 μL, 0.6 mmol) was added to a solution of urea **2a**–**d** (0.5 mmol) in acetonitrile (1 mL) at 0 °C, and the mixture was stirred for 1 h at room temperature. The solvent was evaporated, and the residue was passed through short silica gel pad eluting with EtOAc. The eluent was evaporated, and the residue was dried under vacuum.

*4.4.1. 5,5-Difluoro-4-imino-1-methyl-3,6-diphenyltetrahydropyrimidin-2(1H)-one (**3a**)*

Yield: 150 mg (0.48 mmol, 95%). Mixture of isomers 1.8/1. Colorless crystals. mp 179–181 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.13 (s, 3H), 4.81–4.93 (m, 1H), 7.23–7.63 (m, 10H), 8.22–8.32 (br). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 35.1, 64.5 (dd, J = 26.5, 28.6), 109.2 (dd, J = 246.7, 242.9, major), 110.9 (dd, J = 251.0, 242.7, minor), 127.28, 127.30, 128.4, 128.6, 129.09, 129.14, 129.19, 129.50, 129.58, 129.7, 130.1, 130.7, 130.8, 130.9, 133.9, 136.3, 150.9 (minor), 151.4 (dd, J = 27.6, 24.8, minor), 151.7 (major), 155.6 (dd, J = 32.1, 26.1, major). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −119.0 (d, J = 260.7, minor), −117.7 (d, J = 256.4, major), −98.5 (dd, J = 260.7, 12.7, minor), −98.1 (dd, J = 254.3, 12.7, major). Calcd for $C_{17}H_{15}F_2N_3O$: C, 64.75; H, 4.79; N, 13.33. Found: C, 64.77; H, 4.86; N, 13.33.

*4.4.2. 1-(4-Chlorophenyl)-5,5-difluoro-6-imino-3-methyl-4-phenyltetrahydropyrimidin-2(1H)-one (**3b**)*

Yield: 170 mg (0.49 mmol, 97%). Mixture of isomers 3.4/1. Colorless crystals. mp 164–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.13 (s, 3H), 4.84 (br d, 1H, J = 12.5), 7.18–7.58 (m, 9H), 8.22–8.37 (br). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 35.18 (major), 35.22 (minor), 64.4 (dd, J = 26.5, 28.8), 109.1 (dd, J = 246.5, 243.0) (major), 110.8 (dd, J = 251.1, 243.0, minor), 127.2, 129.2, 129.3, 129.4, 129.7, 129.8, 130.1, 130.4, 130.53, 130.56, 130.62, 130.7, 132.4, 134.3, 134.8, 135.6, 150.7 (minor), 151.1 (dd, J = 27.6, 25.3, minor), 151.5 (major), 155.4 (dd, J = 32.3, 26.5, major). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −119.1 (d, J = 261.2, minor), −117.8 (d, J = 256.4, major), −98.6 (dd, J = 261.2, 12.5, minor), −98.2 (dd, J = 256.4, 12.5, major). HRMS (ESI) Calcd for $C_{17}H_{15}ClF_2N_3O$ (M+H): 350.0866. Found: 350.0863.

*4.4.3. 1-Benzyl-5,5-difluoro-4-imino-3-phenyl-6-thien-2-yltetrahydropyrimidin-2(1H)-one (**3c**)*

Yield: 195 mg (0.49 mmol, 98%). Mixture of isomers 1.6/1. Colorless crystals. mp 142–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.98–4.16 (m, 1H), 4.96–5.09 (m, 1H), 5.44–5.54 (m, 1H), 7.06–7.18 (m, 2H), 7.33–7.64 (m, 11H), 8.36–8.42 (br). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 49.9 (major), 50.0 (minor), 57.3 (dd, J = 30.5, 28.5), 57.8 (t, J = 29.6), 108.7 (dd, J = 247.9, 243.0, major), 110.4 (dd, J = 251.1, 243.6, minor), 127.2, 127.5, 127.61, 127.63, 128.17, 128.20, 128.3, 128.5, 128.58, 128.60, 128.7, 128.9, 129.0, 129.2, 129.29, 129.32, 129.7, 130.3, 133.7 (d, J = 7.5), 134.02 (d, J = 7.5), 134.03 (d, J = 1.1), 135.0, 135.1, 136.4 (d, J = 1.2), 150.5 (minor), 151.1 (dd, J = 27.4, 24.5, minor), 151.5 (major), 155.5 (dd, J = 32.2, 25.9, major). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −118.7 (d, J = 259.7, minor), −117.3 (d, J = 255.4, major), −101.32 (dd, J = 259.7, 10.6, minor), −100.9 (dd, J = 255.4, 10.6, major). HRMS (ESI) Calcd for $C_{21}H_{18}F_2N_3OS$ (M+H): 398.1133. Found: 398.1126.

*4.4.4. 1-Benzyl-3-(4-chlorophenyl)-5,5-difluoro-4-imino-6-thien-2-yltetrahydropyrimidin-2(1H)-one (**3d**)*

Yield: 213 mg (0.49 mmol, 99%). Mixture of isomers 3/1. Colorless crystals. mp 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.98–4.14 (m, 1H), 4.95–5.09 (m, 1H), 5.37–5.50 (m, 1H), 7.04–7.16 (m, 2H), 7.24–7.61 (m, 10H), 8.37–8.45 (br). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 50.0 (major), 50.1 (minor), 57.3 (dd, J = 30.5, 28.5, major), 57.8 (t, J = 29.2, minor), 108.7 (dd, J = 248.2, 243.3, major), 110.3 (dd, J = 251.5, 244.6, minor), 127.3, 127.6, 127.70, 127.73, 128.3, 128.6, 128.7, 128.9, 129.6, 130.2, 130.6, 130.7, 132.5, 134.6, 133.6 (d, J = 7.5), 133.9 (d, J = 8.1), 134.83, 134.85, 135.0, 135.8, 150.3 (minor), 150.9 (dd, J = 27.6, 24.2, minor), 151.3 (major), 155.4 (dd, J = 32.8, 26.5, major). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −118.7 (d, J = 260.7, minor), −117.3 (d, J = 256.4, major), −101.4 (dd, J = 260.7, 10.6, minor), −100.9 (dd, J = 256.4, 10.6, major). HRMS (ESI) Calcd for $C_{21}H_{16}ClF_2N_3OSNa$ (M+Na): 454.0563. Found: 454.0558.

*4.5. 5,5-Difluoro-4-imino-1-methyl-6-phenyl-3-propyltetrahydropyrimidin-2(1H)-one (**3e**)*

DBU (91 mg, 0.6 mmol) was added to a solution of urea **2e** (141 mg, 0.5 mmol) in acetonitrile (1 mL) at 0 °C, and the mixture was stirred for 1 h at room temperature. HCl (5 mL of 0.5M aqueous solution) was added, the mixture was extracted with Et_2O (3 × 3 mL), the combined organic phase was dried (Na_2SO_4), concentrated, and the residue was purified by chromatography (hexanes/EtOAc 3/1). Yield: 110 mg (0.39 mmol, 78%). Mixture of isomers 1.1/1. Colorless oil. R_f 0.51 (hexanes/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.95 (t, 3H, J = 7.7), 1.60–1.78 (m, 2H), 3.03 (s) and 3.08 (s) (3H), 3.75–4.08 (m, 2H), 4.66 (dd, J = 13.0, 2.9) and 4.73 (dd, J = 14.7, 3.8) (1H), 7.11–7.20 (m, 2H), 7.35–7.44 (m, 3H), 8.06–8.24 (br). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.0, 11.10, 20.6, 21.3, 35.1, 35.2, 43.4, 44.3, 64.4 (d, J = 27.1), 64.8 (dd, J = 26.5, 2.6), 108.7 (dd, J = 251.1, 247.0), 109.1 (dd, J = 246.3, 241.7), 127.3 (d, J = 1.6), 127.4 (d, J = 1.6), 129.1, 129.2, 129.6, 129.8, 131.0 (d, J = 6.6), 151.3, 151.9, 154.5 (t, J = 28.2), 159.6 (t, J = 30.3). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −120.4 (d, J = 272.4), −117.5 (d, J = 255.4), −102.1 (dd, J = 272.4, 14.7), −97.6 (dd, J = 255.4, 13.0). HRMS (ESI) Calcd for $C_{14}H_{18}F_2N_3O$ (M+H): 282.1412. Found: 282.1415.

*4.6. 3-(4-Chlorophenyl)-5,5-difluoro-1-methyl-6-phenyldihydropyrimidine-2,4(1H,3H)-dione (**4**)*

HCl (300 μL, 3M aqueous solution) was added to a solution of heterocycle **3b** (175 mg, 0.5 mmol) in dioxane (1 mL), and the

mixture was stirred for 1 h at room temperature. Saturated aqueous Na_2CO_3 (2 mL) was added, and the mixture was extracted with EtOAc (3 × 3 mL). The combined organic phase was dried (Na_2SO_4), and concentrated. The resulting solid was washed with hexane/Et_2O (2/1, 3 mL) and dried under vacuum. Yield: 160 mg (0.46 mmol, 91%). Colorless crystals. mp 149–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.15 (s, 3H), 4.90 (dd, 1H, J = 13.9, 3.7), 7.13–7.22 (m, 2H), 7.37–7.38 (m, 2H), 7.42–7.56 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 35.4, 64.5 (dd, J = 27.1, 25.6), 109.0 (dd, J = 252.8, 247.9), 127.2 (d, J = 1.7), 129.39, 129.47, 129.5, 129.6, 130.1, 132.4, 135.1, 151.0, 159.4 (dd, J = 30.9, 29.9). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −120.3 (d, J = 273.4), −102.8 (dd, J = 273.4, 13.9). HRMS (ESI) Calcd for $C_{17}H_{14}ClF_2N_2O_2$ (M+H): 351.0706. Found: 351.0706.

4.7. 3-(4-Chlorophenyl)-5-fluoro-1-methyl-6-phenylpyrimidine-2,4(1H,3H)-dione (**5**)

Cs_2CO_3 (117 mg, 0.36 mmol) was added to a solution of heterocycle **4** (105 mg, 0.3 mmol) in dimethylformamide (1 mL), and the mixture was stirred for 2 h at 100 °C. The mixture was cooled, diluted with saturated aqueous NH_4Cl (2 mL) and water (3 mL), and extracted with EtOAc (3 × 3 mL). The combined organic phase was dried (Na_2SO_4), concentrated, and the residue was purified by chromatography (hexane/EtOAc, 1/1). Yield: 71 mg (0.21 mmol, 72%). Colorless crystals. mp 232–234 °C (hexanes/EtOAc, 3/1), R_f 0.33 (hexanes/EtOAc 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.20 (s, 3H), 7.19–7.34 (m, 2H), 7.38–7.68 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.3, 127.1 (d, J = 1.7), 128.6 (d, J = 2.3), 129.3, 129.6, 129.7, 130.8, 133.0 (d, J = 1.1), 135.0, 137.6 (d, J = 232.1), 140.0 (d, J = 25.6), 150.5, 156.7 (d, J = 26.5). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −161.2 (s). HRMS (ESI) Calcd for $C_{17}H_{13}ClFN_2O_2$ (M+H): 331.0644. Found: 331.0646.

4.8. 2-Ethyl-4,4-difluoro-3-(4-methoxyphenyl)-3,4-dihydropyrimido[1,6-a]benzimidazol-1(2H)-one (**6e**)

Triethylamine (825 μL, 0.6 mmol) was added to a solution of urea **2j** (243 mg, 0.5 mmol) in acetonitrile (1 mL) at 0 °C, and the mixture was stirred for 1 h at room temperature. The flask was cooled to 0 °C, and HCl (440 μL of 1.7M dioxane solution) was added. The precipitate was filtered, washed with Et_2O, and the combined filtrate was concentrated. The residue was dissolved in dimethylformamide (1 mL) followed by addition of L-proline (30 mg, 0.25 mmol), CuI (10 mg, 0.05 mmol), and Cs_2CO_3 (489 mg, 1.5 mmol). The mixture was stirred for 3 h at 50 °C, then cooled, diluted with water (5 mL) and extracted with EtOAc (3 × 3 mL). The combined organic phase was dried (Na_2SO_4), concentrated, and the residue was purified by chromatography (hexanes/EtOAc, 5/1). Yield: 121 mg (0.34 mmol, 68%). Colorless oil. R_f 0.36 (hexanes/EtOAc 5/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (t, 3H, J = 7.0), 3.12–3.26 (m, 1H), 3.71 (s, 3H), 4.00–4.15 (m, 1H), 4.99 (dd, 1H, J = 12.8, 3.4), 6.80 (d, 2H, J = 8.8), 7.01 (d, 2H, J = 8.8), 7.43 (t, 1H, J = 7.7), 7.52 (t, 1H, J = 7.7), 7.84 (d, 1H, J = 7.7), 8.35 (d, 1H, J = 7.7). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.8, 42.1, 55.2, 65.7 (dd, J = 29.4, 26.8), 111.3 (dd, J = 247.3, 241.6), 114.6, 114.9, 121.2, 122.5 (d, J = 7.2), 125.1, 126.6, 128.7 (d, J = 1.4), 131.8, 142.1 (dd, J = 32.3, 29.7), 142.4, 147.4, 160.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −120.5 (d, J = 269.2), −88.4 (dd, J = 269.2, 12.8). HRMS (ESI) Calcd for $C_{19}H_{18}F_2N_3O_2$ (M+H): 358.1362. Found: 358.1357.

4.9. Synthesis of heterocycles **7** (general procedure)

L-Proline (6.0 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol), and Cs_2CO_3 (489 mg, 1.5 mmol) were added to a solution of urea **2f–j** (0.5 mmol) in dimethylformamide (1 mL). The mixture was stirred at 90 °C during the time given in Table 2. The mixture was cooled, diluted with water (5 mL) and extracted with EtOAc (3 × 3 mL). The combined organic phase was dried (Na_2SO_4), concentrated, and the residue was purified by chromatography (hexanes/EtOAc).

4.9.1. 4-Fluoro-2-methyl-3-phenylpyrimido[1,6-a]benzimidazol-1(2H)-one (**7a**)

Yield: 119 mg (0.41 mmol, 81%). Colorless crystals. mp 212–214 °C (hexanes/EtOAc 10/1). Chromatography (hexanes/EtOAc 3/1), R_f 0.32 (hexanes/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.34 (s, 3H), 7.40–7.62 (m, 7H), 7.88 (d, 1H, J = 8.1), 8.45 (d, 1H, J = 8.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 33.9, 115.1, 119.7, 124.1, 126.0, 127.7, 129.2, 129.4 (d, J = 2.3), 130.4, 130.5, 132.8 (d, J = 26.5), 136.2 (d, J = 235.0), 141.8 (d, J = 30.0), 144.1, 146.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −160.9 (s). Calcd for $C_{17}H_{12}FN_3O$: C, 69.62; H, 4.12; N, 14.33. Found: C, 69.44; H, 4.09; N, 14.37.

4.9.2. 2-Benzyl-4-fluoro-3-thien-2-ylpyrimido[1,6-a]benzimidazol-1(2H)-one (**7b**)

Yield: 150 mg (0.40 mmol, 80%). Yellow crystals. mp 221–223 °C (hexanes/EtOAc 10/1). Chromatography (hexanes/EtOAc 3/1 → 1/1), R_f 0.38 (hexanes/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.23 (s, 2H), 7.00–7.10 (m, 3H), 7.11–7.16 (m, 1H), 7.23–7.31 (m, 3H), 7.45–7.64 (m, 3H), 7.94 (d, 1H, J = 8.1), 8.50 (d, 1H, J = 8.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 49.1, 115.4, 119.9, 124.5, 125.98 (d, J = 1.7), 126.04 (d, J = 25.3), 126.2, 126.6, 124.5, 127.7, 128.6, 129.9, 130.7, 131.8 (d, J = 1.7), 136.2, 137.8 (d, J = 238.4), 141.2 (d, J = 28.8), 144.2, 146.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −154.1 (s). Calcd for $C_{21}H_{14}FN_3OS$: C, 67.18; H, 3.76; N, 11.19. Found: C, 67.31; H, 3.85; N, 11.24.

4.9.3. 4-Fluoro-3-(2-furyl)-2-methylpyrimido[1,6-a]benzimidazol-1(2H)-one (**7c**)

Yield: 110 mg (0.39 mmol, 77%). Colorless crystals. mp 177–179 °C (hexanes/EtOAc 10/1). Chromatography (hexanes/EtOAc 3/1), R_f 0.39 (hexanes/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.50 (s, 3H), 6.62 (br, 1H), 6.91 (br, 1H), 7.37–7.53 (m, 2H), 7.68 (br, 1H), 7.84 (d, 1H, J = 8.1), 8.38 (d, 2H, J = 8.1). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.0, 111.8, 115.1, 116.2 (d, J = 5.8), 119.7, 123.2 (d, J = 23.0), 124.3, 126.0, 130.4, 137.1 (d, J = 241.9), 139.4 (d, J = 3.5), 141.2 (d, J = 28.8), 144.1, 144.9 (d, J = 1.7), 146.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −156.8 (s). Calcd for $C_{15}H_{10}FN_3O_2$: C, 63.60; H, 3.56; N, 14.83. Found: C, 63.49; H, 3.56; N, 14.94.

4.9.4. 4-Fluoro-2-methyl-3-(1-naphthyl)pyrimido[1,6-a]benzimidazol-1(2H)-one (**7d**)

Yield: 136 mg (0.40 mmol, 79%). Colorless crystals. mp 181–183 °C (hexanes/$CHCl_3$ 10/1). Chromatography (hexanes/EtOAc 3/1 → 1/1), R_f 0.40 (hexanes/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.21 (s, 3H), 7.41–7.71 (m, 7H), 7.88–8.09 (m, 2H), 8.47–8.54 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 33.0, 115.1, 119.7, 123.8, 124.2, 124.9, 125.3, 126.0, 126.8, 127.8, 128.6 (d, J = 2.3), 128.8, 130.5, 131.0, 131.1, 131.3 (d, J = 26.5), 133.6, 136.8 (d, J = 234.9), 141.7 (d, J = 29.4), 144.1, 146.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −158.7 (s). Calcd for $C_{21}H_{14}FN_3O$: C, 73.46; H, 4.11; N, 12.24. Found: C, 73.54; H, 4.09; N, 12.21.

4.9.5. 2-Ethyl-4-fluoro-3-(4-methoxyphenyl)pyrimido[1,6-a]benzimidazol-1(2H)-one (**7e**)

Yield: 126 mg (0.37 mmol, 75%). Colorless crystals. mp 185–187 °C (hexanes/EtOAc 10/1). Chromatography (hexanes/EtOAc 5/1 → 3/1), R_f 0.42 (hexanes/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15 (t, 3H, J = 7.0), 3.82–3.94 (m, 2H), 3.85 (s, 3H), 7.05 (d, 2H, J = 8.8), 7.31–7.53 (m, 4H), 7.83 (d, 1H, J = 8.1), 8.41 (d, 1H, J = 8.1).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0, 41.2, 55.3, 114.5, 115.1, 119.3, 119.5, 123.8, 125.8, 130.4, 130.8 (d, J = 2.3), 132.5 (d, J = 26.5), 136.3 (d, J = 232.6), 141.7 (d, J = 29.9), 144.0, 146.2, 160.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −160.0 (s). HRMS (ESI) Calcd for $C_{19}H_{17}FN_3O_2$ (M+H): 338.1299. Found: 338.1289.

Acknowledgments

This work was supported by the Ministry of Science (project MD-4750.2013.3), and the Russian Academy of Sciences (program #8). We thank Dr. B. Lichitskii for helpful discussions.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2013.06.018.

References

[1] (a) I. Ojima (Ed.), Fluorine in Medicinal Chemistry and Chemical Biology, John Wiley & Sons, Chichester, 2009;
(b) J.-P. Begue, D. Bonnet-Delpon, Bioorganic and Medicinal Chemistry of Fluorine, Wiley-VCH, Weinheim, 2008.
[2] (a) C. Isanbor, D. O'Hagan, J. Fluorine Chem. 127 (2006) 303–319;
(b) V.A. Petrov (Ed.), Fluorinated Heterocyclic Compounds, John Wiley & Sons, Hoboken, 2009.
[3] (a) S. Ozaki, Med. Res. Rev. 16 (1996) 51–86;
(b) J.S. de Bono, C.J. Twelves, Invest. New Drugs 19 (2001) 41–59.
[4] For uracils bearing fluorinated alkyl substituent, see:
(a) S. Fustero, J.F. Sanz-Cervera, A. Simon-Fuentes, R. Roman, S. Catalan, M. Murguoa, Fluorinated Heterocycles, American Chemical Society, 2009 , pp. 182–209;
(b) S. Fustero, J. Piera, J.F. Sanz-Cervera, S. Catalan, C. Ramirez de Arellano, Org. Lett. 6 (2004) 1417–1420.
[5] (a) M.J. Robins, S.R. Naik, J. Am. Chem. Soc. 93 (1971) 5277–5278;
(b) R.H. Hesse, D.H.R. Barton, H.T. Toh, M.M. Pechet, J. Org. Chem. 37 (1972) 329–330;
(c) G.W.M. Visser, S. Boele, B.W. Van Halteren, G.H.J.N. Knops, J.D.M. Herscheid, G.A. Brinkman, A. Hoekstra, J. Org. Chem. 51 (1986) 1466–1471;
(d) S. Stavber, M. Zupan, Tetrahedron 46 (1990) 3093–3100;
(e) G.S. Lal, W. Pastore, R. Pesaresi, J. Org. Chem. 60 (1995) 7340–7342.
[6] For an overview of chemistry of fluorinated five- and six-membered heterocycles, see:
A.W. Erian, J. Heterocycl. Chem. 38 (2001) 793–808.
[7] F. Olimpieri, S. Fustero, A. Volonterio, M. Zanda, Synthesis (2010) 651–660.
[8] M.D. Kosobokov, A.D. Dilman, V.V. Levin, M.I. Struchkova, J. Org. Chem. 77 (2012) 5850–5855.
[9] For non-fluorinated analogous process, *ortho*-cyanoanilines have been mainly employed as 1,4-bipolar system, see:
(a) J.W. Chern, P.L. Tao, M.H. Yen, G.Y. Lu, C.Y. Shiau, Y.J. Lai, S.L. Chien, C.H. Chan, J. Med. Chem. 36 (1993) 2196–2207;
(b) S. Richter, B. Gioffreda, Arch. Pharm. 344 (2011) 810–820;
(c) N. Haider, G. Heinisch, R. Wanko, J. Heterocycl. Chem. 28 (1991) 1441–1444.
[10] CCDC-934724 (**3a**) and CCDC-934723 (**7a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[11] (a) D. Ma, Q. Cai, Acc. Chem. Res. 41 (2008) 1450–1460;
(b) G. Evano, N. Blanchard, M. Toumi, Chem. Rev. 108 (2008) 3054–3131.
[12] For alternative preparative methods of pyrimido[1,6-*a*]benzimidazol-1(2*H*)-ones, see:
(a) K. Takagi, T. Aotsuka, Morita, Y. Hikari, Okamoto, J. Heterocycl. Chem. 23 (1986) 1443–1449;
(b) P. Molina, M. Alajarin, A. Vidal, Tetrahedron 45 (1989) 4263–4286;
(c) X. Zhao, D.-Q. Shi, J. Heterocycl. Chem. 47 (2010) 524–527;
For biological studies of heterocycles of this type, see:
(d) I. Linhart, P. Mikes, E. Frantik, J. Mraz, Chem. Res. Toxicol. 24 (2011) 383–391.
[13] S.J. Hays, B.W. Caprathe, J.L. Gilmore, N. Amin, M.R. Emmerling, W. Michael, R. Nadimpalli, R. Nath, K.J. Raser, D. Stafford, D. Watson, K. Wang, J.C. Jaen, J. Med. Chem. 41 (1998) 1060–1067.
[14] V.V. Levin, A.D. Dilman, P.A. Belyakov, M.I. Struchkova, V.A. Tartakovsky, Eur. J. Org. Chem. (2008) 5226–5230.